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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/785,951	02/16/2001	Michael John Mullan	01097.0008U2	7348

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	PAPER NUMBER
1632	13

DATE MAILED: 03/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/785,951	MULLAN, MICHAEL JOHN	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicant's arguments filed December 19, 2002 in paper no. 12 have been fully considered but they are not persuasive. The amendments have been entered.

The amendments to claims 25-28,31 and 32 have overcome the rejected made under 35 U.S.C. 112, first paragraph in the office action mailed June 13, 2002 in paper no.7.

The amendments to claims 25-32 have overcome the rejected under 35 U.S.C. § 112, second paragraph in the office action mailed June 13, 2002 in paper no. 7.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 25-28 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11 and 12 of U.S. Patent No. 5,455,169 for reasons presented in the office action mailed June 13, 2002 in paper no.7. Although the conflicting claims are not identical, they are not patentably distinct from each other because the specific nucleic acid sequences claimed in claims 11 and 12 of '169 are encompassed within the scope of claims 25-28 in the instant claims.

Applicant states that they will either cancel claims 25-28 or file a terminal disclaimer once a Notice of Allowability is received. This argument is not persuasive as allowance cannot be decided until all rejections have been overcome. If the obviousness-type double

patenting is the only remaining rejection, allowance cannot be determined. Applicant must satisfy the rejection prior to allowance.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-24,29 and 30 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons presented in the office action mailed June 13, 2002 in paper no.7.

Claims 21-24, 29 and 30 are drawn to non-human transgenic animals comprising in a germ or somatic cells a nucleic acid characteristic of human amyloid precursor protein including the nucleotides encoding codon 670 and 671 of human amyloid precursor protein, operably linked to a promoter, wherein the amino acid encodes at amino acid 670 other than lysine and/or at amino acid 671 other than methionine, and wherein the animal expresses the human amyloid precursor protein or fragment thereof which encodes an amino acid other than lysine at codon 670 and/or an amino acid other than methionine at codon 671, and wherein the animal comprises a nucleic acid that further encodes other than valine at amino acid 717, wherein in the mouse exhibits neuropathological characteristics of Alzheimer's Disease, and methods of screening agents capable of treating Alzheimer's disease comprising contacting an agent with the transgenic non-human animal and monitoring the expression, processing or deposition of amyloid precursor protein or fragments thereof.

Applicant argues that the specification discloses the methodology to produce a transgenic mouse, and discloses vectors that can be used in the production of the mouse.

Applicant argues that the specification states more than that the transgene can be merely integrated into the mouse genome. Applicant argues that they have disclosed the use of the neural-specific enolase promoter to regulate expression of the mutant APP having the Swedish mutation. Applicant argues that they have taught the skilled artisan how to make the constructs, how to prepare the DNA form the vectors for injection into the nonhuman animal recipient, and how to deliver the transgene to a one-cell embryo. Applicant argues that they have taught the stage embryo for transplantation and the analysis of tail DNA to detect integration of the transgene. Applicant argues that transgenic animal production was routine at the time of filing as evidence by the allowance of US Patent 4,873,191 (Wagner). Applicant argues that Quon et al is evidence to the routine nature of producing a transgenic mouse that manifests neuropathologic signs of Alzheimer's Disease. Applicant argues that Quon used a rate NSE promoter to direct expression of APP751 to obtain amyloid protein deposits in the brain of the mice. Applicant argues that additional evidence for the production of transgenic mice expressing APP751 DNA sequences and forming amyloid deposits can be found in US Patent 5,387,742. Applicant argues that their methodology parallels that of '742 and Quon, indicating the routineness of the method. Applicant argues that the skill level in the area of transgenic animals was high, and that the skilled artisan expected to perform a significant amount of experimentation to obtain the transgenic animal of interest. Applicant argues that their invention can be used as a screening assay to determine compounds that affect amyloid processing. Applicant cites US Patent 5,720,936 as evidence for such a use. Applicant argues that their transgenic mouse can be used for the same assay. Applicant argues that such an assay doesn't require amyloid deposits. Applicant refers to US Patents 5,877,399 and 5,894,078 as evidence that the production of transgenic animals was routine at the time of filing. As further evidence applicant has supplied Li et al which discloses a transgenic animal that expresses human APP770 and the

animal exhibits amyloid deposits in the cortical and hippocampal brain regions. These arguments are not persuasive.

The means through which to produce any transgenic animal at the time of the present invention, 1992, is not the issue. The issue turns on whether or not the specification provides guidance on producing transgenic animal that has a use in the art as taught by the specification. Applicant's specification states that the transgenic animal can be used to study the progression of Alzheimer's disease, to identify treatments and drugs that alter the degenerative progress, arrest the development or reverse the progression of Alzheimer's disease, and to identify environmental factors that affect the onset of Alzheimer's disease (specification, page 4, parag. 3 and 4). This use requires that the animal develop a pathogenesis specific for Alzheimer's disease. The expression of the encoded protein would not be so specific. Even the development of amyloid plaques would not rise to the level of an enabled use for the animal as at the time of filing amyloid plaques were known to develop in aged humans and aged monkeys (Selkoe, page 432, col. 1, parag. 3, lines 1-10).). Unless the animal continues from β-amyloid plaque formation to more Alzheimer's disease related pathologies, the animal would not have a use under applicant's disclosure. While applicant's specifically disclosed mice may express human APP, it is the development of Alzheimer's related pathologies that is unpredictable and is what is required for use in studying Alzheimer's disease progression and factors that affect progression or cause inhibition of Alzheimer's disease.

Further, while the papers of Quon and Li, and US patents 5,387,742, 5,720,936, 5,877,399 and 5,894,078 each disclose mice that express an APP transgene, they do not support the enablement of applicant's claims as the mice disclosed either do not develop Alzheimer's disease related pathologies, or the promoter and/or construct used was not disclosed in applicant's specification. For example in Quon and US Patent 5,387,742, the

mice expressing a wild-type APP sequence develop β-amyloid deposits but do not develop any pathology related to Alzheimer's disease. Further, US Patent 5,720,936 discloses a particular exon/intron cDNA APP constructs and a PDGF promoter not disclosed in the present specification, US Patent discloses the use of the prion promoter, not disclosed in the present specification and US Patent 5,894,078 discloses the β-actin promoter, not disclosed in the present specification. Each of these patents required inventive efforts not disclosed in the present specification to achieve the production of transgenic mice that exhibited a phenotype associated with Alzheimer's disease so that these mice can be used to study the progression of Alzheimer's disease, factors that affect the progression and treatment protocols that can prevent, reverse or inhibit the progress. If the mice or animal only develops plaques, this is not sufficient to serve as a model as disclosed since plaques alone are not indicative of Alzheimer's disease.

It is also important to note that the specification never discloses any particular phenotype of Alzheimer's that the animals are to develop so that the artisan does not know what phenotype to assay for when implementing the invention. With particular reference to US Patent 7,720,936 (Wadsworth), the present specification does not disclose a use of the animals in determining factors that affect APP processing. Applicant should point specifically to a place in the specification where there is disclosure for the use of a mouse or animal that expresses the DNA encoding APP-Swedish where the animal develops plaques or that the animal can be used to assay factors affecting APP processing. The examiner cannot find such a disclosure. Applicant must contemplate the invention at the time of filing, and cannot decide post-filing that which is the invention.

Applicant argues that the prior disclosures of transgenic animals expressing APP isoforms would have lead the skilled artisan to find the novel Swedish mutant interchangeable and to expect that take advantage of the fact that the Swedish mutant

produces high levels of β-amyloid. Applicant cites US Patent 5,877,399 (Hsiao) as evidence for the high level of expression. These arguments are not persuasive

Hsiao ('399) used the prion promoter to direct expression of the Swedish mutant DNA sequence. This sequence is not contemplated or disclosed by the present specification. Further, the art teaches that an NSE – APPSwe did not express at sufficient levels to produce transgenic mice that expressed APPSwe sufficiently to produce amyloid-β deposition, neuronal disorganization or reactive gliosis up to the age of one year (Malherbe, col. 1, parag. 1, lines 22-26 and page 209, col. 2. parag. 1, lines 7-9). Thus, the art supports the lack of enablement rejection.

Applicant argues that the examiner has misapplied Kappell. Kappell, it is argued, only states that methylation may be a problem and that somatic cell deletion may be a problem. Applicant argues that the examiner is incorrect in stating that cellular mechanisms are present that prevent expression of the transgene. Applicant argues that Kappell teaches that transgenic technology is well established as a critical method for analyzing gene expression and function. Applicant also states that reference to Kappell is incorrect because Kappell doesn't discuss APP transgenes and that there have been many patents issued to APP transgenic mice. This argument is not persuasive.

For a reference to support an argument of unpredictability, the reference is no required to state that never can a transgenic animal be produced. The reference, as does Kappell, needs to set forth reasoning as to why the production of transgenic animals is unpredictable. Since there is no means to control where the transgene inserts into the genome of the animal, it is unpredictable as to whether the transgene will be silenced or deleted from the genome. The present specification offers no methodology to overcome the unpredictable site of transgene insertion. The fact that there are patents to transgenic mice

expressing a particular transgene is not relevant. Each application is examined on its own merits, and those merits do not cross-over to other applications.

Applicant also argues that the examiner has misapplied Lannfelt, and that Lannfelt discloses that mutant APP sequences are more likely to lead to β-amyloid depositions. This argument is not persuasive. This is not persuasive.

Lannfelt does not state that the mutant APP isoforms will result in mice exhibiting Alzheimer's disease pathologies, only that they are more likely since they are associated with the disease.

Applicant argues that the examiner has misapplied Higgins, and that Higgins taught that mice expressing APP751 did manifest neuropathologies associated with Alzheimer's disease. This argument is not persuasive.

This variation in result in Higgins, that APP695 did not support amyloid deposit formation but APP751 did supports the unpredictability of the presently claimed invention at the time of filing. This clearly indicates that the out come of APP expression cannot be predicted.

Applicant argues that problems anticipated by the use of the APP695 isoform are overcome by the showing in Hsiao ('399) of APP695 mice having Alzheimer's disease pathologies. Applicant argues that Hsiao demonstrates that mice as a species being resistant to expressing a mutant APP gene is not supported. These arguments are not persuasive.

Hsiao used a transgene construct where the prion promoter directed expression of several APP transgenes including APP695 and APP695-Swedish. It is not possible to discern if the Alzheimer's disease pathologies were due to the DNA sequence or the promoter. However, since Malherbe stated that NSE-APP695Swe mice did not develop β-amyloid

deposition, it is reasonable to conclude that the prion promoter is the agent that brought the particular Alzheimer's pathologies observed in the Hsiao mice.

Applicant argues that Felsenstein maybe technically correct but is incorrect in stating that no animal model exists that can recapitulate the pathological cascade of Alzheimer's Disease. Applicant argues that the Quon mouse is a credible model for studying the neuropathology of Alzheimer's Disease. Applicant argues that it was recognized in the art and the patent office that a useful model may allow the study of APP processing without necessarily recapitulating the cascade of Alzheimer's disease. Also, applicant argues that Felsenstein recognizes that rats may not be the proper models for Alzheimer's disease and alternative species may be more prone to initiation of amyloidosis. Applicant argues that older rats may have shown amyloid deposits, but they were not examined. Applicant argues that because older rats were not examined that Felsenstein is not relevant art. These arguments are not persuasive.

Felsenstein clear teaches that transgenic rats did not produce β-amyloid deposits. There is no guidance in the specification that older rats would have such deposits. Felsenstein's lack of analysis of older rats does not negate the teaching in Felsenstein that rats failed to produce deposits. Further, the uses for the animals of the claims have to come from the art. What the patent office allowed or what the art taught does not provide uses for applicant's transgenic animals. It is up to applicant to recognize the invention and so disclose such. Applicant cannot decide and state post-filing what the invention is. As there is no disclosure for the use of the animals to study APP processing, applicant cannot at this point say that is their invention. Further the art has stated that the production of AD type amyloid expression may be only possible for certain mouse strains as in AA amyloid inflammation can only be obtained in certain mouse strains, and not in Syrian hamsters or rats (Greenberg, page 162, col. 2, parag. 1). Thus art questions the use of mouse strains

and other rodents for the production of Alzheimer's Disease models at the time of filing. As for non-rodent species, it is reasonable to extrapolate that the production of an Alzheimer's disease model in these animals is also unpredictable based on the rodent studies.

Applicant argues that they are not required to demonstrate that the claimed transgenic mice have β-amyloid deposits in their brains, that they are only required to provide credible evidence. Applicant argues that their specification read in light of the art leads to that level of evidence. Applicant argues that the office has not provided a scientific basis as to why the claimed mice cannot be used for the purposes disclosed. These arguments are not persuasive.

Applicant has misread the rejection if they believe a request for producing the animals has been made. However, the art at the time of filing clear teaches that the production of transgenic animals as models for Alzheimer's Disease was unpredictable. Especially noteworthy is the teachings of Malherbe that one of applicant's specific embodiments failed to produce deposits, leading to a clear lack of enablement. Further, applicant's disclosed use for the animals requires more than deposits as deposits are found in many aged primates, including humans so that for an animal to have a use to study Alzheimer's disease progression or treatment of the disease, the animal would necessarily need to have a phenotype more than mere deposit of β-amyloid.

The claims are free of the prior art. At the time of the instant invention, the prior art did not disclose or suggest a nucleic acid that encoded a human amyloid precursor protein where an amino acid other than lysine was at position 670 or an amino acid other than methionine was at position 671. Thus the prior art did not make or suggest transgenic non-human animal or isolated mammalian cells that expressed this nucleic acid sequence, or a method of screening using either the transgenic non-human animal or the cells.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 7/23/02 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 609(B)(2)(i). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 703-308-1126. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9306 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

dc
March 4, 2003